Insulin-Secreting Cystosarcoma Phyllodes of the Breast: A Case Report and Literature Review

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Introduction

Tumor hypoglycemia is most commonly associated with insulinomas secondary to insulin production by the islet-cell tumor.[1] Insulinomas are the most common pancreatic endocrine neoplasms, with an incidence of one case per million per year.[2] They are rarely ectopic, with almost 100% of documented tumors occurring within the pancreas. The majority occur sporadically (> 90%) and are solitary.[3] Lesions occurring in the setting of multiple endocrine neoplasia (MEN) type I syndrome constitute approximately 5% of cases and may be multicentric within the pancreas.[2]

Almost all affected patients have symptoms due to hypoglycemia and adhere to Whipple's triad consists of: (1) symptomatic hypoglycemia induced by fasting, (2) glucose levels less than 50 mg/dL, and (3) relief of symptoms with administration of glucose.[4] These criteria are fundamental for establishing the diagnosis of insulinoma; however, they may also be used to indicate that presenting symptoms, in general, are caused by severe hypoglycemia.[1] In addition to insulinomas, symptoms may arise from non-islet-cell tumors.[1] Doege reported the first case in 1930 when he described a patient with a large fibrosarcoma and hypoglycemia. Since that time, a number of similar cases have been described in the literature.[5] These tumors are generally large, slow-growing, mesenchymal tumors (e.g. sarcomas, fibromas, mesotheliomas, or hemangiopericytomas) located in the retroperitoneum or thorax.[6] The underlying mechanism of hypoglycemia appears to be the production of peptides with insulin-like structure and bioactivity that exerts an effect on the insulin receptor.[1]

We describe a unique patient who presented with hypoglycemia and a rapidly enlarging breast mass. Surgical resection revealed a cystosarcoma phyllodes tumor with insulin-secreting epithelial cells. We believe this to be the first reported case of a breast mass causing severe non-islet-cell tumor hypoglycemia.

Case Report

A 33-year-old, nulliparous, Marshallese female presented to Majuro Hospital in March, 2000 with complaints of generalized weakness. At that time, she was found to be profoundly hypoglycemic. The hypoglycemia responded only to infusion of D_{10}, with occasional need for D_{50} boluses. She had no history of diabetes mellitus and denied taking any medications. Initial evaluation also revealed massive enlargement of the left breast. She denied having any pain or constitutional symptoms. The patient's mother reported having noticed the enlargement only 3 weeks earlier; however, sufficient details regarding the breast enlargement were difficult to obtain secondary to the patient's mental derangement and the mother's poor history. Apart from her mental illness, the patient had no significant past medical history. She had always been short and small, but otherwise developed normally until the age of 27 when her mental status deteriorated abruptly. She stopped taking care of her personal hygiene, often showing no interest in eating or her own safety. Her sister had visited the Marshall Island within the past year and had not noticed any breast enlargement at that time. Menarche was at age 15 and she reported regular monthly cycles. There was no family history of breast or ovarian cancers.

The patient was air evacuated to Tripler Army Medical Center, where she was promptly taken to Emergency Room for deterioration of her mental status. She was severely obtunded with questionable airway compromise. On arrival, her serum glucose level was 55 mg/dL. Following an infusion of D_{50}, her glucose levels remained low at 24 mg/dL. Additional glucose replacement finally succeeded in normalizing her levels with subsequent improvement of her mental status. During her hospitalization, normal glucose levels could not be sustained with regular meals; therefore, she was started on a D_{10} infusion, which was titrated to maintain euglycemia.

On physical examination, the left breast was massively enlarged (Figure 1). There was a firm, freely mobile, non-tender mass involving all four quadrants of the breast. The overlying skin was shiny with mild hyperemia and visible, dilated veins. No discharge was noted from either breast. Examination of the right breast revealed two discrete, firm, mobile 1 cm nodules in the upper outer quadrant. No axillary, supraclavicular, or infraclavicular lymphadenopathy was noted. Examination of her skin revealed extremely small hands and feet with multiple old scars on her lower extremities bilaterally and lesions on her upper extremities in various states of healing. Remainder of the physical examination was unremarkable.

The patient's laboratory work-up was significant for: normal liver function tests and pancreatic enzymes, a glucose of 25 mg/dL and insulin level of 39 μU/mL while fasting, C-peptide = 0.4 ng/mL, Insulin-like Growth Factor (IGF)-I = 59 ng/mL, Insulin-like Growth Factor (IGF)-II = 330 ng/mL, a random cortisol level of 8.8 μg/dL, and a TSH = 1.62 μIU/mL.

Mammography showed diffuse enlargement of the left breast. A core needle biopsy demonstrated that the mass was consistent with fibroadenoma vs. cystosarcoma phyllodes tumor. Abdominal ultrasound revealed a normal liver, gallbladder, and pancreas. CT scan of the abdomen/pelvis, including her pancreas, did not show any abnormalities.

She was taken for simple mastectomy on 15 May 2000. A firm, irregular, lobulated mass measuring 18 x 16.5 x 11.5 cm was excised. Each lobule had a papillary appearance surrounded by a thick fibrous rim with prominent vascular channels. The cut surfaces exuded a scant amount of gelatinous to highly viscous clear fluid as well

Figure 1.— Picture of a massively enlarged left breast.

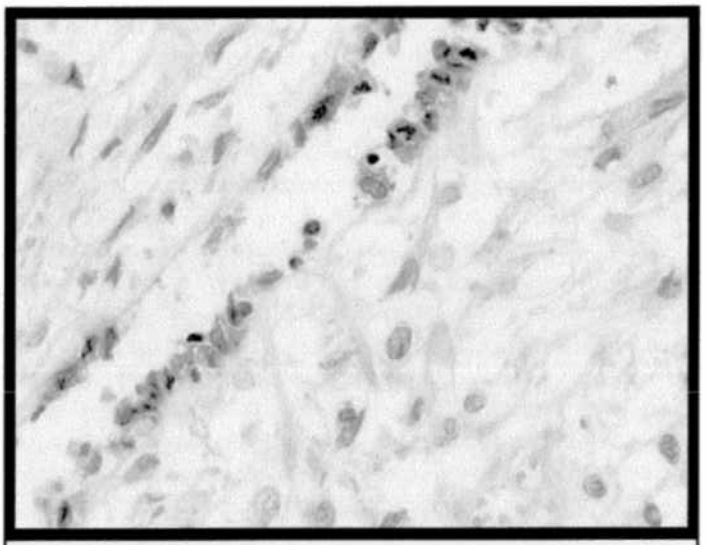

Figure 2.— Positive immunohistochemical staining of epithelial cells in the cystosarcoma phylloides.

as multiple areas of chocolate brown, distorted sacs. Pathologic examination classified the mass as a massive, low-grade phyllodes tumor. Sections showed the tumor to be composed of broad leaf-like processes with spindled, mildly cellular stroma without cytologic atypia and only rare mitotic figures. Immunohistochemical stains for insulin were focally positive in the epithelial cells (Figure 2). Immunostains for CK903 and smooth muscle actin were also evaluated and revealed a mosaic pattern of staining in the hyperplastic epithelium within the tumor.

The patient did well postoperatively with resolution of her hypoglycemia. She was discharged on post-operative day 3. She has had no evidence of hypoglycemia to date, on follow-up.

Discussion

We report a patient with a large, well-differentiated cystosarcoma phyllodes tumor who presented with a history significant for weakness, altered mental status in the fasted state, and symptoms consistent with Whipple's triad. The differential diagnosis for such a patient is relatively focused. Drug-induced hypoglycemia was unlikely as our patient was on no medications. Normal C-peptide levels ruled-out factitious hypoglycemia. Thus, we focused on the patient's tumor as the likely culprit.

The majority of insulinomas are less than 2 cm, benign, and solitary.[7] They are almost exclusively intrapancreatic, with approximately 75% of tumors being located in the body and tail of the pancreas, to the left of the superior mesenteric artery.[8] This distribution seems to correspond to the normal distribution of insulin cells within the pancreas. However, up to ten percent of insulinomas are malignant, and thus, metastatic.[7] Metastases are found most commonly in the surrounding lymph nodes and liver. Furthermore, multicentric lesions are found in the majority of patients with MEN I syndrome. Radiological studies in our patient failed to detect any suspicious masses in the pancreas; therefore, we suspected her breast mass to be the primary source of her symptoms.

Ectopic insulinomas are exceptionally rare. A retrospective study by the Mayo Clinic examined the institution's sixty-year experience with insulinoms from 1927 to 1986.[9] This investigation described only one ectopic tumor in a cohort of 194 patients.[9] Although the specific location of this tumor was not discussed, the surgical procedures for all patients in the study were intraabdominal, suggesting its development within the abdomen. No ectopic insulinomas were reported in additional studies that encompassed over three decades of clinical experience.[10,11] A Medline literature review from the years 1902 to 2003 found no record of an insulinoma presenting as a breast mass.

Core biopsies of the patient's breast mass indicated that it was likely a cystosarcoma phyllodes, an uncommon fibroepithelial neoplasm of the breast that accounts for 0.3-0.9% of all breast cancers in females.[12] Although similar in structure to a fibroadenoma, the tumor may be distinguished histologically by large leaf-like projections of stroma with increased stromal cellularity.[12] The biological behavior of these tumors is highly variable, and the criteria for differentiating between malignant and benign neoplasms remain poorly defined. Surgery is the primary mode of treatment. Although radical mastectomy was performed in the past, more conservative approaches are now recommended. Currently, the choice is made between wide local excision with ≥ 1 cm margins vs. simple mastectomy without axillary clearance.[12] While recurrences are not uncommon with these lesions, a number of recent studies have shown that wide local excision with negative margins yields local control rates of approximately 90%.[13] Due to the large size of the tumor in our patient, we elected to perform a simple mastectomy. Pathologic review revealed a cystosarcoma phyllodes tumor with insulin-secreting epithelial cells. The absence of islet-cells suggested that this mass, although insulin-secreting, was not of pancreatic origin, and thus was not an ectopic insulinoma.

Although non-islet-cell tumor hypoglycemia (NICTH) has been reported in several neoplasms of mesodermal and epithelial origin, to our knowledge, there have been no cases of NICTH in patients with cystosarcoma phyllodes.[1] The tumors tend to be large and

well-differentiated, as in our patient. However, patients with NICTH generally demonstrate low or unmeasureable levels of serum insulin during hypoglycemic episodes. Recent studies have explained this paradox by suggesting that peptides with an insulin-like structure, especially insulin-like growth factor (IGF)-II and an incompletely processed IGF-II propeptide ("big" IGF-II), may be responsible.[1] In contrast to this typical presentation of NICTH, our patient was found to have elevated insulin levels as well as decreased levels of IGF-I and IGF-II. Histological evaluation of the tumor demonstrated insulin-secreting cells.

Medical treatment for insulinomas and NICTH-causing lesions is generally either palliative or used only while awaiting surgical excision of the lesion.[11] Surgical therapy is typically curative and continued hypoglycemia following tumor resection is suspicious for the presence of multicentric lesions or metastases. Surgery is also the mainstay of treatment for patients with cystosarcoma phyllodes. Our case is interesting in that etiology of our patient's hypoglycemia was an insulin-secreting cystosarcoma phyllodes. Furthermore, histological and laboratory evaluation revealed that the lesion was neither a true ectopic insulinoma, nor was it typical of a NICTH-causing tumor. Despite these unique characteristics, definitive treatment was straightforward. Simple mastectomy of the affected breast provided complete resection of neoplastic tissue in addition to resolution of the patient's hypoglycemia. In the end, this case serves to illustrate another rare, but plausible, culprit in the differential of tumor-induced hypoglycemia.

This article contains the opinions of the authors only and does not represent the opinions of the United States Department of Defense or the United States Army.

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